Guidance for Industry

Container Closure Systems for Packaging Human Drugs and Biologics

CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 1999

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U.S. Department of Health and Human Services
Food and Drug Administration
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Center for Biologics Evaluation and Research (CBER)
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GUIDANCE FOR INDUSTRY[1]

CONTAINER CLOSURE SYSTEMS FOR PACKAGING HUMAN DRUGS AND BIOLOGICS

CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION

I. INTRODUCTION

This document is intended to provide guidance on general principles[2] for submitting information on packaging materials used for human drugs and biologics.[3] This guidance supersedes the FDA *Guideline for Submitting Documentation for Packaging for Human Drugs and Biologics*, issued in February 1987 and the packaging policy statement issued in a letter to industry dated June 30, 1995 from the Office of Generic Drugs.[4] This guidance is not intended to describe the information that should be provided about packaging operations associated with drug product manufacture.

Approaches which differ from those described in this guidance may be followed, but the applicant is encouraged to discuss significant variations in advance with the appropriate CDER chemistry review staff or CBER review staff. This is to prevent applicants or sponsors from spending unnecessary time and effort in preparing a submission that the FDA may later determine to be unacceptable.

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[1] This guidance has been prepared by the Packaging Technical Committee of the Chemistry, Manufacturing, and Controls Coordinating Committee (CMC CC) in the Center for Drug Evaluation and Research (CDER) and in conjunction with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on container closure systems for the packaging of human drugs and biological products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

[2] In general, this guidance does not suggest specific test methods and acceptance criteria (except for references to *The United States Pharmacopia* methods), nor does it suggest comprehensive lists of tests. These details should be determined based on good scientific principles for each specific container closure system for particular drug product formulations, dosage forms, and routes of administration. Acceptance criteria should be based on actual data for particular packaging components and container closure systems, and they should be set to ensure batch-to-batch uniformity of packaging components.

[3] As used in this guidance, the terms *drug* and *drug product* include biologics unless otherwise noted.

[4] The policy statement is a document titled *Container/Closure Information Which Should Be Provided In An ANDA/AADA* which was written by the Office of Generic Drugs/Packaging Advisory Group.

II. BACKGROUND

The Federal Food, Drug, and Cosmetic Act (the Act) mandates the need for adequate information related to packaging materials. Section 501(a)(3) of the Act states that a drug is deemed to be adulterated "if its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health...." In addition, section 502 of the Act states that a drug is considered misbranded if there are packaging omissions. Also, section 505 of the Act requires a full description of the methods used in, and the facilities and controls used for, the packaging of drugs (see Attachment A).

Section 505(b)(1)(D) of the Act states that an application shall include a full description of the methods used in, the manufacturing, processing and packing of such drug. This includes facilities and controls used in the packaging a drug product.

A. Definitions[5]

Materials of construction[6] refer to the substances (e.g., glass, high density polyethylene (HDPE) resin, metal) used to manufacture a packaging component.

A *packaging component* means any single part of a container closure system. Typical components are containers (e.g., ampules, vials, bottles), container liners (e.g., tube liners), closures (e.g., screw caps, stoppers), closure liners, stopper overseals, container inner seals, administration ports (e.g., on large-volume parenterals (LVPs)), overwraps, administration accessories, and container labels. A *primary packaging component* means a packaging component that is or may be in direct contact with the dosage form. A *secondary packaging component* means a packaging component that is not and will not be in direct contact with the dosage form.

A *container closure system* refers to the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. A *packaging system* is equivalent to a container closure system.

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[5] These definitions are intended to clarify the use of certain terms in this guidance only and are not intended to supersede the definitions of *container* and *package* as provided for in 21 CFR 600.3.

[6] This term is used in a general sense for the basic material, which should be defined in the application in terms of its specific chemical composition for a given drug application (e.g., the specific polymer and any additives used to make the material).

A *package* or *market package*[7] refers to the container closure system and labeling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons or shrink wrap). A market package is the article provided to a pharmacist or retail customer upon purchase and does not include packaging used solely for the purpose of shipping such articles.

Quality refers to the physical, chemical, microbiological, biological, bioavailability, and stability attributes that a drug product should maintain if it is to be deemed suitable for therapeutic or diagnostic use. In this guidance, the term is also understood to convey the properties of safety, identity, strength, quality, and purity (see 21 CFR 211.94(a)).

An *extraction profile* refers to the analysis (usually by chromatographic means) of extracts obtained from a packaging component. A *quantitative extraction profile* is one in which the amount of each detected substance is determined.

B. CGMP, CPSC and USP Requirements on Containers and Closures

Current good manufacturing practice (CGMP) requirements for the control of drug product containers and closures are included in 21 CFR Parts 210 and 211. A listing of the relevant sections is provided in Attachment A. In addition, a listing of Compliance Policy Guides that deal with packaging issues is provided in Attachment B. References in this guidance to CGMP regulations are provided for completeness. For additional information, refer to the *FDA Compliance Program Guidance Manual* for Pre-Approval Inspections/Investigations (7346.832) which describes specific responsibilities for CDER scientists and for field investigators.

The FDA requirement for tamper-resistant closures is included in 21 CFR 211.132 and the Consumer Product Safety Commission (CPSC) requirements for child-resistant closures are included in 16 CFR 1700. An outline of these and other applicable regulatory requirements is provided in Attachment A.

The United States Pharmacopeial Convention has established requirements for containers which are described in many of the drug product monographs in *The United States Pharmacopeia/National Formulary* (USP/NF). For capsules and tablets, these requirements generally relate to the design characteristics of the container (e.g., tight, well-closed or light-resistant). For injectable products, materials of construction are also addressed (e.g., "Preserve in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light"). These requirements are defined in the "General Notices and Requirements" (Preservation, Packaging, Storage, and Labeling) section of the *USP*. The requirements for materials of construction are defined in the "General Chapters" of

[7] The materials of construction used in the labeling are a concern from a packaging perspective if they affect the protection and/or safety of the drug product.

the USP (see Attachment A).

C. Additional Considerations

1. Submissions of INDs

The packaging information in the chemistry, manufacturing, and controls section of an IND usually includes a brief description of the components, the assembled packaging system and any precautions needed to ensure the protection and preservation of the drug substance and drug product during their use in the clinical trials.

For general guidance regarding the container closure system information to be submitted for phase 1 studies, refer to the FDA guidance for industry *Content and Format of investigational New Drug Applications(INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products* (November 1995).

General guidance regarding the container closure system information to be submitted for phase 2 or phase 3 studies will be provided in the FDA guidance for industry *INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products, Chemistry, Manufacturing, and Controls Content and Format,* when finalized (draft guidance published April 21, 1999).

2. Submissions on Packaging of a Drug Product by Another Firm

a. Contract Packager

A contract packager is a firm retained by the applicant to package a drug product. The applicant remains responsible for the quality of the drug product during shipping, storage, and packaging.

The information regarding the container closure system used by a contract packager that should be submitted in the CMC section of an application (NDA, ANDA, or BLA), or in a DMF which is referenced in the application, is no different from that which would be submitted if the applicant performed its own packaging operations. If the information is provided in a DMF, then a copy of the letter of authorization (LOA) for the DMF should be provided in the application (see section V.A).

b. Repackager[8]

A repackager is a firm that buys drug product from the drug product manufacturer or distributor and repackages it for sale under a label different from that of the manufacturer. The repackager is responsible for ensuring the quality and stability of the repackaged drug prpoduct. The repackaging operation is required to e in compliance with CGMPs (21 CFR Part 211), and there are limits to the expiration period that may be used with the repackaged product unless the repackager conducts stability studies.[9] Packaging qualification information is not required if the repackager uses the same container closure system approved in the original application.

All significant phases of the manufacturing and processing of a drug product (including packaging) should be described as part of the CMC section of an application (NDA, ANDA or BLA), or in a DMF referenced in the application. The only exception is the repackaging of solid oral drug products for which an approved application already exists.[10] For biologics, repackaging is considered a step in the manufacturing process for which licensing is required (21 CFR 600.3(u) and 601).

III. QUALIFICATION AND QUALITY CONTROL OF PACKAGING COMPONENTS

A. Introduction

CDER and CBER approve a container closure system to be used in the packaging of a human drug or biologic as part of the application (NDA, ANDA or BLA) for the drug or biologic. A packaging system found acceptable for one drug product is not automatically assumed to be appropriate for another. Each application should contain enough information to show that each proposed container closure system and its components are suitable for its intended use.

The type and extent of information that should be provided in an application will depend on the dosage form and the route of administration. For example, the kind of information that should be provided about a packaging system for an injectable dosage form or a drug

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[8] This discussion does not apply to the repackaging of drug products for dispensing under the practice of pharmacy.

[9] FDA *Compliance Policy Guides*, "Expiration Dating of Unit Repackaged Drugs," 480.200, February 1, 1984, rev. March 1995 (CPG 7132b.11).

[10] FDA *Compliance Policy Guides*, "Regulatory Action Regarding Approved New Drugs and Antibiotic Drug Products Subjected to Additional Processing or Other Manipulation," 446.100, January 18, 1991 (CPG 7132c.06).

product for inhalation is often more detailed than that which should be provided about a packaging system for a solid oral dosage form. More detailed information usually should be provided for a liquid-based dosage form than for a powder or a solid, since a liquid-based dosage form is more likely to interact with the packaging components.

Table 1 illustrates the correlation between the degree of concern regarding the route of administration with the likelihood of packaging component-dosage form interactions for different classes of drug products.

Table 1
Examples of Packaging Concerns for Common Classes of Drug Products

Degree of Concern Associated with the Route of Administration	**Likelihood of Packaging Component-Dosage Form Interaction**		
	High	**Medium**	**Low**
Highest	Inhalation Aerosols and Solutions; Injections and Injectable Suspensions[a]	Sterile Powders and Powders for Injection; Inhalation Powders	
High	Ophthalmic Solutions and Suspensions; Transdermal Ointments and Patches; Nasal Aerosols and Sprays		
Low	Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions	Topical Powders; Oral powders	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules

[a] For the purposes of this table, the term *suspension* is used to mean a mixture of two immiscible phases (e.g., solid in liquid or liquid in liquid). As such, it encompasses a wide variety of dosage forms such as creams, ointments, gels, and emulsions, as well as suspensions in the pharmaceutical sense.

For the purpose of this guidance, container closure systems for the most common types of dosage forms will be discussed in terms of five general categories: Inhalation Drug Products (section III.D); Drug Products for Injection and Ophthalmic Drug Products (Section III.E); Liquid-based Oral and Topical Drug Products and Topical Delivery Systems (section III.F); Solid Oral Dosage Forms and Powders for Reconstitution (section

III.G); and Other Dosage Forms (section III.H).

B. General Considerations

Suitability refers to the tests and studies used and accepted for the initial qualification of a component or a container closure system for its intended use. *Quality control* (QC) refers to the tests typically used and accepted to establish that, after the application is approved, the components and the container closure system continue to possess the characteristics established in the suitability studies. The subsections on *associated components* and *secondary components* describe the tests and studies for establishing suitability and quality control for these types of components. However, the ultimate proof of the suitability of the container closure system and the packaging process is established by full shelf life stability studies.

1. Suitability for the Intended Use

Every proposed packaging system should be shown to be *suitable* for its intended use: it should adequately *protect* the dosage form; it should be *compatible* with the dosage form; and it should be composed of materials that are considered *safe* for use with the dosage form and the route of administration. If the packaging system has a *performance* feature in addition to containing the product, the assembled container closure system should be shown to function properly.

Information intended to establish suitability may be generated by the applicant, by the supplier of the material of construction or the component, or by a laboratory under contract to either the applicant or the firm. An adequately detailed description of the tests, methods, acceptance criteria, reference standards, and validation information for the studies should be provided. The information may be submitted directly in the application or indirectly by reference to a DMF. If a DMF is used, a letter authorizing reference (i.e., letter of authorization (LOA)) to the DMF must be included in the application (see section V.A).

General issues concerning protection, compatibility, safety and performance of packaging components and/or systems are discussed below. In this guidance, component functionality and drug delivery will also be addressed in connection with specific dosage forms and routes of administration (see sections III.D, III.E, III.F, III.G, and III.H).

a. Protection

A container closure system should provide the dosage form with adequate protection from factors (e.g., temperature, light) that can cause a degradation in the quality of that dosage form over its shelf life. Common causes of such degradation are: exposure to light, loss of solvent, exposure

to reactive gases (e.g., oxygen), absorption of water vapor, and microbial contamination. A drug product can also suffer an unacceptable loss in quality if it is contaminated by filth.

Not every drug product is susceptible to degradation by all of these factors. Not all drug products are light sensitive. Not all tablets are subject to loss of quality due to absorption of moisture. Sensitivity to oxygen is most commonly found with liquid-based dosage forms. Laboratory studies can be used to determine which of these factors actually have an influence on a particular drug product.

Light protection[11] is typically provided by an opaque or amber-colored container or by an opaque secondary packaging component (e.g., cartons or overwrap). The USP test for light transmission (USP <661>) is an accepted standard for evaluating the light transmission properties of a container. Situations exist in which solid and liquid-based oral drug products have been exposed to light during storage because the opaque secondary packaging component was removed, contrary to the approved labeling and the USP monograph recommendation. A firm, therefore, may want to consider using additional or alternate measures to provide light protection to these drug products when necessary.

Loss of solvent can occur through a permeable barrier (e.g., a polyethylene container wall), through an inadequate seal, or through leakage. Leaks can develop through rough handling or from inadequate contact between the container and the closure (e.g., due to the buildup of pressure during storage). Leaks can also occur in tubes due to a failure of the crimp seal.

Water vapor or reactive gases (e.g., oxygen) may penetrate a container closure system either by passing through a permeable container surface (e.g., the wall of a low density polyethylene (LDPE) bottle) or by diffusing past a seal. Plastic containers are susceptible to both routes. Although glass containers would seem to offer better protection, because glass is relatively impermeable, glass containers are more effective only if there is a good seal between the container and the closure.

Protection from microbial contamination is provided by maintaining adequate container integrity after the packaging system has been sealed. An adequate and validated procedure should be used for drug product manufacture and packaging.

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[11] For further information regarding photostability studies, see the FDA *Guideline for the Photostability Testing of New Drug Substances and Products* (May 1997).

b. Compatibility

Packaging components that are compatible with a dosage form will not interact sufficiently to cause unacceptable changes in the quality of either the dosage form or the packaging component.

Examples of interactions include loss of potency due to absorption or adsorption of the active drug substance, or degradation of the active drug substance induced by a chemical entity leached from a packaging component; reduction in the concentration of an excipient due to absorption, adsorption or leachable-induced degradation; precipitation; changes in drug product pH; discoloration of either the dosage form or the packaging component; or increase in brittleness of the packaging component.

Some interactions between a packaging component and dosage form will be detected during qualification studies on the container closure system and its components. Others may not show up except in the stability studies. Therefore, any change noted during a stability study that may be attributable to interaction between the dosage form and a packaging component should be investigated and appropriate action taken, regardless of whether the stability study is being conducted for an original application, a supplemental application, or as fulfillment of a commitment to conduct postapproval stability studies.

c. Safety

Packaging components should be constructed of materials that will not leach harmful or undesirable amounts of substances to which a patient will be exposed when being treated with the drug product. This consideration is especially important for those packaging components which may be in direct contact with the dosage form, but it is also applicable to any component from which substances may migrate into the dosage form (e.g., an ink or adhesive).

Making the determination that a material of construction used in the manufacture of a packaging component is safe for its intended use is not a simple process, and a standardized approach has not been established. There is, however, a body of experience which supports the use of certain approaches that depend on the route of administration and the likelihood of interactions between the component and the dosage form (see Table 1).

For a drug product such as an injection, inhalation, ophthalmic, or transdermal, a comprehensive study is appropriate. This involves two

parts: first, an extraction study[12] on the packaging component to determine which chemical species may migrate into the dosage form (and at what concentration); and, second, a toxicological evaluation of those substances which are extracted to determine the safe level of exposure via the label specified route of administration. This technique is used by the Center for Food Safety and Applied Nutrition (CFSAN) to evaluate the safety of substances that are proposed as indirect food additives (e.g., polymers or additives that may be used in for packaging foods).[13]

The approach for toxicological evaluation of the safety of extractables should be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing).

For many injectable and ophthalmic drug products (see sections III.E and III.F), data from the USP Biological Reactivity Tests and USP Elastomeric Closures for Injections tests will typically be considered sufficient evidence of material safety.

For many solid and liquid oral drug products, an appropriate reference to the indirect food additive regulations (21 CFR 174-186) promulgated by CFSAN for the materials of construction used in the packaging component will typically be considered sufficient. Although these regulations do not specifically apply to materials for packaging drug products, they include purity criteria and limitations pertaining to the use of specific materials for packaging foods that may be acceptable for the evaluation of drug product packaging components. Applicants are cautioned that this approach may not be acceptable for liquid oral dosage forms intended for chronic use (see section III.F.1).

For drug products that undergo clinical trials, the absence of adverse reactions traceable to the packaging components is considered supporting evidence of material safety.

Safety assessments for specific dosage forms are discussed further in section III of this guidance.

d. Performance

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[12] See Attachment C for discussion of extraction studies.

[13] FDA/CFSAN, *Recommendations for Chemistry Data for Indirect Food Additive Petitions*, Version 1.2, Chemistry Review Branch, Office of Pre-Market Approval, June 1995.

Performance of the container closure system refers to its ability to function in the manner for which it was designed. A container closure system is often called upon to do more than simply contain the dosage form. When evaluating performance, two major considerations are container closure system functionality and drug delivery.

i. Container Closure System Functionality

The container closure system may be designed to improve patient compliance (e.g., a cap that contains a counter), minimize waste (e.g., a two-chamber vial or IV bag), improve ease of use (e.g., a prefilled syringe), or have other functions.

ii. Drug Delivery

Drug delivery refers to the ability of the packaging system to deliver the dosage form in the amount or at the rate described in the package insert. Some examples of a packaging system for which drug delivery aspects are relevant are a prefilled syringe, a transdermal patch, a metered tube, a dropper or spray bottle, a dry powder inhaler, and a metered dose inhaler.

Container closure system functionality and/or drug delivery are compromised when the packaging system fails to operate as designed. Failure can result from misuse, faulty design, manufacturing defect, improper assembly, or wear and tear during use. Tests and acceptance criteria regarding dosage form delivery and container closure system functionality should be appropriate to the particular dosage form, route of administration, and design features.

e. Summary

Table 2 summarizes typical packaging suitability considerations for common classes of drug products.

Table 2
Typical Suitability Considerations for Common Classes of Drug Products
(This table is a general guide, and is not comprehensive. See sections III.C through III.H for a more detailed discussion.)

Route of Administration/ Dosage Form	SUITABILITY[a]			
	Protection	**Compatibility**	**Safety**	**Performance/ Drug Delivery**
Inhalation Aerosols and Solutions, Nasal Sprays	L, S, M, W, G	Case 1c	Case 1s	Case 1d
Inhalation Powders	L, W, M	Case 3c	Case 5s	Case 1d
Injections, Injectable Suspensions[b]	L, S, M, G	Case 1c	Case 2s	Case 2d
Sterile Powders and Powders for Injection	L, M, W	Case 2c	Case 2s	Case 2d
Ophthalmic Solutions and Suspensions	L, S, M, G	Case 1c	Case 2s	Case 2d
Topical Delivery Systems	L, S	Case 1c	Case 3s	Case 1d
Topical Solutions and Suspensions, and Topical and Lingual Aerosols	L, S, M	Case 1c	Case 3s	Case 2d
Topical Powders	L, M, W	Case 3c	Case 4s	Case 3d
Oral Solutions and Suspensions	L, S, M	Case 1c	Case 3s	Case 2d
Oral Powders	L, W	Case 2c	Case 3s	Case 3d
Oral Tablets and Oral (Hard and Soft Gelatin) Capsules	L, W	Case 3c	Case 4s	Case 3d

[a] If there is a special performance *function* built into the drug product (e.g., counter cap), it is of importance for any dosage form/route of administration to show that the container closure system performs that function properly.

[b] For definition of the term *suspension*, see footnote a to Table 1.

Explanation of Codes in Table 2:

Protection:	**L** (protects from light, if appropriate) **S** (protects from solvent loss/leakage) **M** (protects sterile products or those with microbial limits from microbial contamination) **W** (protects from water vapor, if appropriate) **G** (protects from reactive gases, if appropriate)
Compatibility:	**Case 1c**: Liquid-based dosage form that conceivably could interact with its container closure system components (see examples described in section III.B.1). **Case 2c**: Solid dosage form until reconstituted; greatest chance for interacting with its container closure system components occurs after it is reconstituted. **Case 3c**: Solid dosage form with low likelihood of interacting with its container closure system components.
Safety:	**Case 1s**: Typically provided are USP Biological Reactivity Test data, extraction/toxicological evaluation, limits on extractables, and batch-to-batch monitoring of extractables. **Case 2s**: Typically provided are USP Biological Reactivity Test data and possibly extraction/toxicological evaluation. **Case 3s**: Typically, an appropriate reference to the indirect food additive regulations is sufficient for drug products with aqueous-based solvents. Drug products with non-aqueous based solvent systems or aqueous based systems containing co-solvents generally require additional suitability information (see section III.F). **Case 4s**: Typically, an appropriate reference to the indirect food additive regulations is sufficient. **Case 5s:** Typically, an appropriate reference to the indirect food additive regulations for all components except the mouthpiece for which USP Biological Reactivity Test data is provided.
Performance:	**Case 1d**: Frequently a consideration. **Case 2d**: May be a consideration. **Case 3d**: Rarely a consideration.

2. Quality Control of Packaging Components

In addition to providing data to show that a proposed container closure system is suitable for its intended use, an application should also describe the quality control measures that will be used to ensure consistency in the packaging components (see section III.C.3). These controls are intended to limit unintended postapproval

variations in the manufacturing procedures or materials of construction for a packaging component and to prevent adverse affects on the quality of a dosage form.

Principal consideration is usually given to consistency in physical characteristics and chemical composition.

a. Physical Characteristics

The physical characteristics of interest include dimensional criteria (e.g., shape, neck finish, wall thickness, design tolerances), physical parameters critical to the consistent manufacture of a packaging component (e.g., unit weight), and performance characteristics (e.g., metering valve delivery volume, or the ease of movement of syringe plungers). Unintended variations in dimensional parameters, if undetected, may affect package permeability, drug delivery performance, or the adequacy of the seal between the container and the closure. Variation in any physical parameter is considered important if it can affect the quality of a dosage form.

b. Chemical Composition

The chemical composition of the materials of construction may affect the safety of a packaging component. New materials[14] may result in new substances being extracted into the dosage form or a change in the amount of known extractables. Chemical composition may also affect the compatibility, functional characteristics or protective properties of packaging components by changing rheological or other physical properties (e.g., elasticity, resistance to solvents, or gas permeability).

A composition change may occur as a result of a change in formulation or in a processing aid (e.g., using a different mold release agent) or through the use of a new supplier of a raw material. A change in the supplier of a polymeric material or a substance of biological origin is more likely to bring with it an unexpected composition change than a change in the supplier of a pure chemical compound, because polymeric and natural materials are often complex mixtures. A composition change may also occur with a change in the manufacturing process, such as the use of different operating conditions (e.g., a significantly different curing temperature), different equipment, or both.

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[14] These are substances not previously determined to be safe by extraction/toxicological evaluation studies (e.g., the USP Biological Reactivity Tests or another appropriate method conducted on the packaging component as part of the qualifying process).

A change in formulation is considered a change in the specifications for the packaging component. This change in the formulation of a packaging component by its manufacturer should be reported to the firm that purchases that component and to any appropriate DMF. The firm that purchases the component should, in turn, report the change to its application as required under 21 CFR 314.70(a) or 601.12. Manufacturers who supply a raw material or an intermediate packaging component should inform their customers of any intended changes to formulations or manufacturing procedures and update the DMF in advance of implementing such a change. Changes which seem innocuous may have unintended consequences on the dosage form marketed in the affected packaging system.

The use of stability studies for monitoring the consistency of a container closure system in terms of compatibility with the dosage form and the degree of protection provided to the dosage form is accepted. Currently there is no general policy concerning the monitoring of a packaging system and components with regard to safety. One exception involves inhalation drug products for which batch-to-batch monitoring of the extraction profile for the polymeric and elastomeric components is routine.

3. Associated Components

Associated components are packaging components that are typically intended to deliver the dosage form to the patient but are not stored in contact with the dosage form for its entire shelf life. These components are packaged separately in the market package and are either attached to the container upon opening or used only when a dose is to be administered. Measuring spoons, dosing cups, measuring syringes, and vaginal delivery tubes are examples of associated components that typically contact the dosage form only during administration. A hand pump or dropper combined into a closure are examples of an associated component that would contact the dosage form from the time the packaging system is opened until the dosing regimen is completed.

The complete and assembled component and its parts should meet suitability criteria appropriate for the drug product and the actual use of the component (see sections III.B.1 and III.B.2). Safety and functionality are the most common factors to be established for suitability. The length of time that the associated component and the dosage form are in direct contact should also be taken into consideration when assessing the suitability of an associated component.

4. Secondary Packaging Components

Unlike primary and associated packaging components, *secondary packaging components* are not intended to make contact with the dosage form. Examples are cartons, which are generally constructed of paper or plastic, and overwraps, which may be fabricated from a single layer of plastic or from a laminate made of metal foil, plastic, and/or paper.

A secondary packaging component generally serves one or more of the following additional functions:

a. Provides protection from excessive transmission of moisture or solvents into or out of the packaging system

b. Provides protection from excessive transmission of reactive gases (atmospheric oxygen, inert headspace filler gas, or other organic vapors) into or out of the packaging system

c. Provides light protection for the packaging system

d. Provides protection for a packaging system that is flexible or needs extra protection from rough handling

e. Provides an additional measure of microbiological protection (i.e., by maintaining sterility or by protecting the packaging system from microbial intrusion)

When information on a container closure system is submitted in an application, the emphasis would normally be on the primary packaging components. For a secondary packaging component, a brief description will usually suffice unless the component is intended to provide some additional measure of protection to the drug product. In this case, more complete information should be provided, along with data showing that the secondary packaging component actually provides the additional protection (see sections III.B.1 and III.B.2).

Because secondary packaging components are not intended to make contact with the dosage form, there is usually less concern regarding the materials from which they are constructed. However, if the packaging system is relatively permeable, the possibility increases that the dosage form could be contaminated by the migration of an ink or adhesive component, or from a volatile substance present in the secondary packaging component. (For example, a solution packaged in a LDPE container was found to be contaminated by a volatile constituent of the secondary packaging components that enclosed it.). In such a case, the secondary packaging component should be considered a potential source of contamination and the safety of its materials of construction should be taken into consideration.

C. Information That Should Be Submitted in Support of an Original Application for Any Drug Product[15]

Additional discussion and information regarding the CMC information to be provided in an application (NDA, ANDA, or BLA) can be found in the guidances and guidelines listed in Attachment E.

1. Description

A general description of the entire container closure system should be provided in the CMC section of the application. In addition, the following information should be provided by the applicant for each individual component of the packaging system:

a. Identification by product name, product code (if available), the name and address of the manufacturer, and a physical description of the packaging component (e.g., type, size, shape, and color)

b. Identification of the materials of construction (i.e., plastics, paper, metal, glass, elastomers, coatings, adhesives, and other such materials) should be identified by a specific product designation (code name and/or code number) and the source (name of the manufacturer).[16] Alternate materials of construction should also be indicated. Postconsumer recycled plastic should not be used in the manufacture of a primary packaging component. If used for a secondary or associated component, then the safety and compatibility of the material for its intended use should be addressed appropriately.

c. Description of any operations or preparations that are performed on a packaging component by the applicant (such as washing, coating, sterilization, or depyrogenation)[17]

2. Information About Suitability

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[15] See Table 3 for additional information. This section applies to primary packaging components and to those associated and secondary packaging components that provide protection to the drug product or for which there may be a safety concern (see section III.B).

[16] Where possible, this information should be included in the application. Alternatively, it may be provided in a drug master file (see section V) and a letter of authorization (LOA) to the DMF submitted in the application. The LOA permits the Agency to review the information in support of a particular application.

[17] For further information see the FDA guidance for industry *Submission of Documentation for the Sterilization Process Validation in Applications of Human and Veterinary Drug Products* (November 1994).

a. To establish safety and to ensure consistency, the complete chemical composition should be provided for every material used in the manufacture of a packaging component.

b. Test results from appropriate qualification and characterization tests should be provided. Adequate information regarding the tests, methods, acceptance criteria, reference standards, and validation information should be provided.

To address protection, use of USP tests (see Attachment A) for light transmission, moisture permeation, microbial limits, and sterility are generally considered sufficient. Testing for properties other than those described in USP (e.g., gas transmission, solvent leakage container integrity) may also be necessary.

To address safety and compatibility, the results of extraction/toxicological evaluation studies should be provided for drug products that are likely to interact with the packaging components and introduce extracted substances into the patient (see Table 1). For drug products less likely to interact, other tests (e.g., USP Biological Reactivity Test) or information (e.g., appropriate reference to the indirect food additive regulations at 21 CFR 174-186) could be used to address the issue of safety and compatibility (see Table 2). For example, an appropriate reference to an indirect food additive regulation is generally sufficient for a solid oral dosage form product.

To address performance, the results of USP and non-USP functionality tests are considered sufficient if the test and acceptance criteria are appropriate for the intended purpose.

Tests described in the USP are typically considered sufficient standards for establishing specified properties and characteristics of specified materials of construction or packaging components.

For non-USP tests, an applicant should provide justification for the use of the test, a complete and detailed description of how the test was performed, and an explanation of what the test is intended to establish. If a related USP test is available, comparative data should be provided using both methods. Supporting data should include a demonstration of the suitability of the test for its intended use and its validation.

Testing on an assembled container closure system is usually

performed by the applicant (or a testing laboratory commissioned by the applicant) and the test results provided in the application. Such tests may include vacuum leak testing, moisture permeation, and weight loss or media fill.

Testing on an individual packaging component is typically performed by the manufacturer of the component and reported via a DMF (see section V).

3. Information About Quality Control

The fabricator/manufacturer of a packaging component and the drug product manufacturer who uses this firm share the responsibility for ensuring the quality of packaging components. These firms should have a quality control program in place so that consistent components are produced. The drug product manufacturer must have an inspection program for incoming packaging components and materials (21 CFR 211.22, 211.84 and 211.122). For most drug products, a drug product manufacturer may accept a packaging component lot based on receiving a Certificate of Analysis (COA) or Certificate of Certification (COC) from the component supplier and the performance of an appropriate identification test, provided the supplier's test data are periodically validated (21 CFR 211.84(d)(3)). Acceptance of a packaging component lot based on a supplier's COA or COC may not be appropriate in all cases (e.g., some packaging components for certain inhalation drug products).

a. Applicants

The tests and methods used by the applicant for acceptance of each batch of a packaging component that they receive should be described. If a batch is to be accepted based on a supplier's COA or COC, then the procedure for supplier validation should be described. The data from the supplier's COA or COC should clearly indicate that the lot meets the applicant's acceptance criteria. Acceptance criteria for extractables should also be included, if appropriate.

Dimensional and performance criteria should be provided. Dimensional information is frequently provided via a detailed schematic drawing complete with target dimensions and tolerances and may be provided via the packaging component manufacturer's DMF. A separate drawing may not be necessary if the packaging component is part of a larger unit for which a drawing is provided or if the component is uncomplicated in design (e.g., a cap liner).

b. Manufacturers of Packaging Components Sold to Drug Product

Manufacturers

Each manufacturer of a packaging component sold to a drug product manufacturer should provide a description of the quality control measures used to maintain consistency in the physical and chemical characteristics of the component. These generally include release criteria (and test methods, if appropriate) and a description of the manufacturing procedure. If the release of the packaging component is based on statistical process control,[18] a complete description of the process (including control criteria) and its validation should be provided.

The description of the manufacturing process is generally brief and should include any operations performed on the packaging component after manufacture but prior to shipping (e.g., washing, coating, and/or sterilization). In some cases it may be desirable for the description to be more detailed and to include in-process controls.

This information may be provided via a DMF (see section V).

c. Manufacturers of Materials of Construction or of Packaging Components Used to Make Other Packaging Components

The quality control procedures of the manufacturer of a packaging component may sometimes rely in whole or in part on the quality control procedures of a manufacturer who makes an intermediate packaging component that is used to create the component. If so, each contributor to the final packaging system should provide a description of the quality control measures used to maintain consistency in the physical and chemical characteristics of the separate components and of the assembled packaging system that they provide.

The manufacturer of each material of construction should be prepared to describe the quality control measures used to maintain consistency in the chemical characteristics of their product.

This information may be provided via a DMF (see section V).

4. Stability Data (Packaging Concerns)

Stability testing of the drug product should be conducted using the container

[18] Statistical process control is defined as "[t]he application of statistical techniques for measuring and analyzing the variation in processes." Juran, J.M., ed., 1988, *Quality Control Handbook*, 4th ed., McGraw-Hill, p. 24.2.

closure systems proposed in the application. The packaging system used in each stability study should be clearly identified.

The container closure system should be monitored for signs of instability. When appropriate, an evaluation of the packaging system should be included in the stability protocol. Even when a formal test for quality of the packaging system is not performed, the applicant should investigate any observed change in the packaging system used in the stability studies. The observations, results of the investigation, and corrective actions should be included in the stability report. If the corrective action requires a change in an approved container closure system, a supplemental application should be submitted.

For general guidance on conducting stability studies, refer to the FDA *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987). The stability guideline is undergoing revision and will be superseded by the FDA's draft guidance for industry *Stability Testing of Drug Substance and Drug Products* (June 1998), once it is issued in final form.

Table 3
Information That Should Be Submitted in an Original Application for Any Drug Product

Description	Overall general description of the container closure system, plus: For Each Packaging Component: • Name, product code, manufacturer, physical description • Materials of construction (for each: name, manufacturer, product code) • Description of any additional treatments or preparations
Suitability	Protection: (By each component and/or the container closure system, as appropriate) • Light exposure • Reactive gases (e.g., oxygen) • Moisture permeation • Solvent loss or leakage • Microbial contamination(sterility/container integrity, increased bioburden, microbial limits) • Filth • Other Safety: (for each material of construction, as appropriate) • Chemical composition of all plastics, elastomers, adhesives, etc.[a] • Extractables, as appropriate for the material[b] Extraction/toxicological evaluation studies, as appropriate Appropriate USP testing Appropriate reference to the indirect food additive regulations (21 CFR 174-186) • Other studies as appropriate Compatibility: (for each component and/or the packaging system, as appropriate) • Component/dosage form interaction, USP methods are typically accepted • May also be addressed in post-approval stability studies Performance: (for the assembled packaging system) • Functionality and/or drug delivery, as appropriate
Quality Control	For Each Packaging Component Received by the Applicant: • Applicant's tests and acceptance criteria[c] • Dimensional (drawing) and performance criteria • Method to monitor consistency in composition, as appropriate For Each Packaging Component Provided by the Supplier: • Manufacturer's acceptance criteria for release, as appropriate • Brief description of the manufacturing process
Stability	• See section III.C.4

[a] Including any additives used in the manufacture of a packaging component

[b] See Attachment C for further discussion of extraction studies. Testing of plastics should be performed on the packaging component, not on the unformed resin. For a blow/fill/seal product, extractables should be evaluated on the formed drug product container itself. This also applies to a container closure system which is manufactured as part of the drug product manufacturing process.

[c] Note that an applicant's acceptance tests may include, among others, test parameters indicated under the description, suitability, and quality control sections of this table.

D. Inhalation Drug Products

Inhalation drug products include inhalation aerosols (metered dose inhalers); inhalation solutions, suspensions, and sprays (administered via nebulizers); inhalation powders (dry powder inhalers); and nasal sprays. The CMC and preclinical considerations for inhalation drug products are unique in that these drug products are intended for respiratory-tract compromised patients. This is reflected in the level of concern given to the nature of the packaging components that may come in contact with the dosage form or the patient (see Table 1).

Guidance regarding the container closure system information to support the approval of applications for inhalation drug products will be provided in two guidance documents when finalized: the guidance for industry *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products; Chemistry, Manufacturing and Controls Documentation* (a draft was issued in October 1998) and the guidance for industry *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products; Chemistry, Manufacturing and Controls Documentation,* which is currently under development.

E. Drug Products for Injection and Ophthalmic Drug Products

These dosage forms share the common attributes that they are generally solutions, emulsions, or suspensions, and are all required to be sterile. Injectable dosage forms represent one of the highest risk drug products (see Table 1). Any contaminants present (as a result of contact with a packaging component or due to the packaging system's failure to provide adequate protection) can be rapidly and completely introduced into the patient's general circulation. Although the risk factors associated with ophthalmics are generally considered to be lower than for injectables, any potential for causing harm to the eyes demands caution.

1. Injectable Drug Products

Injectable drug products may be liquids in the form of solutions, emulsions, suspensions, or dry solids that are to be combined with an appropriate vehicle to yield a solution or suspension. Injections are classified as small-volume parenterals (SVPs), if they have a solution volume of 100 mL or less, or as large-volume parenterals (LVPs), if the solution volume exceeds 100 mL.[19] For solids that must be dissolved or dispersed in an appropriate diluent before being injected, the diluent may be in the same container closure system (e.g., a two-part vial) or be part of the same market package (e.g., a kit containing a vial of diluent).

[19] The terms SVP and LVP as used in this guidance correspond to the definitions of small-volume injection and large-volume injection, respectively, in USP 23, page 1650.

An SVP may be packaged in a disposable cartridge, a disposable syringe, a vial, an ampule or a flexible bag. An LVP may be packaged in a vial, a flexible bag, a glass bottle or, in some cases, as a disposable syringe.

Cartridges, syringes, vials, and ampules are usually composed of Type I or II glass, or polypropylene. Flexible bags are typically constructed with multilayered plastic. Stoppers and septa in cartridges, syringes, and vials are typically composed of elastomeric materials. The input (medication) and output (administration) ports for flexible bags may be plastic and/or elastomeric materials. An overwrap may be used with flexible bags to retard solvent loss and to protect the flexible packaging system from rough handling.

The potential effects of packaging component/dosage form interactions are numerous. Hemolytic effects may result from a decrease in tonicity and pyrogenic effects may result from the presence of impurities. The potency of the drug product or concentration of the antimicrobial preservatives may decrease due to adsorption or absorption. A cosolvent system essential to the solubilization of a poorly soluble drug can also serve as a potent extractant of plastic additives. A disposable syringe may be made of plastic, glass, rubber, and metal components, and such multicomponent construction provides a potential for interaction that is greater than when a container consists of a single material.

Injectable drug products require protection from microbial contamination (loss of sterility or added bioburden) and may also need to be protected from light or exposure to gases (e.g., oxygen). Liquid-based injectables may need to be protected from solvent loss, while sterile powders or powders for injection may need to be protected from exposure to water vapor. For elastomeric components, data showing that a component meets the requirements of USP Elastomeric Closures for Injections will typically be considered sufficient evidence of safety. For plastic components, data from USP Biological Reactivity Tests will typically be considered sufficient evidence of safety. Whenever possible, the extraction studies should be performed using the drug product. If the extraction properties of the drug product vehicle may reasonably be expected to differ from that of water (e.g., due to high or low pH or due to a solubilizing accipient), then drug product should be used as the extracting medium. If the drug substance significantly affects extraction characteristics, it may be necessary to perform the extractions using the drug product vehicle. If the total of extracts significantly exceeds the amount obtained from water extraction, then an extraction profile should be obtained. It may be advisable to obtain a quantitative extraction profile of an elastomeric or plastic packaging component and to compare this periodically to the profile from a new batch of the packaging component. Extractables should be identified whenever possible. For a glass packaging component, data from USP Containers: Chemical Resistance — Glass Containers will typically be considered sufficient evidence of safety and compatibility. In some cases (e.g., for some chelating

agents), a glass packaging component may need to meet additional criteria to ensure the absence of significant interactions between the packaging component and the dosage form.

Performance of a syringe is usually addressed by establishing the force to initiate and maintain plunger movement down the barrel, and the capability of the syringe to deliver the labeled amount of the drug product.

2. Ophthalmic Drug Products

These drug products are usually solutions marketed in a LDPE bottle with a dropper built into the neck (sometimes referred to as *droptainer*), or ointments marketed in a metal tube with an ophthalmic tip (see section III.F.2 for a more detailed discussion of tubes). A few solution products use a glass container due to stability concerns regarding plastic packaging components. Ophthalmic ointments that are reactive toward metal may be packaged in a tube lined with an epoxy or vinyl plastic coating. A large volume intraocular solution (for irrigation) may be packaged in a glass or polyolefin (polyethylene and/or polypropylene) container.

The American Academy of Ophthalmology (AAO) recommended to the Agency that a uniform color coding system be established for the caps and labels of all topical ocular medications. An applicant should either follow this system or provide an adequate justification for any deviations from the system. The AAO color codes, as revised and approved by the AAO Board of Trustees in June 1996, are shown in Table 5.

Although ophthalmic drug products can be considered topical products (section III.F.2), they have been grouped here with injectables because they are required to be sterile (21 CFR 200.50(a)(2)) and the descriptive, suitability, and quality control information is typically the same as that for an injectable drug product. Since ophthalmic drug products are applied to the eye, compatibility and safety should also address the container closure system's potential to form substances which irritate the eye or introduce particulate matter into the product (see USP <771> Ophthalmic Ointments).

See Table 4 for additional information.

Table 4
Information That Typically Should Be Submitted for Injectable or Ophthalmic Drug Products

Description	Overall general description of container closure system, plus: For Each Packaging Component: • Name, product code, manufacturer, physical description • Materials of construction (for each: name, manufacturer and product code) • Description of any additional treatments (e.g., procedures for sterilizing and depyrogenating packaging components)
Suitability	Protection: (By each component and/or the container closure system, as appropriate) • Light exposure, when appropriate • Reactive gases (e.g., oxygen) • Moisture permeation (powders) • Solvent loss (liquid-based dosage forms) • Sterility (container integrity) or increased bioburden • Seal integrity or leak testing of tubes (ophthalmics) Safety: (for each material of construction, as appropriate) • Chemical composition of all plastics, elastomers, adhesives, etc.[a] • For elastomeric closures: USP Elastomeric Closures for Injections testing • For glass components: USP Containers: Chemical Resistance — Glass Containers • For plastic components and coatings for metal tubes: USP Biological Reactivity Tests • If the extraction properties of the drug product vehicle may reasonably be expected to differ from that of water (e.g., due to high or low pH or due to a solubilizing excipient), then drug product should be used as the extracting medium. • If the total weight of extracts significantly exceeds the amount obtained from water extraction, then an extraction profile should be obtained. • For plastic or elastomeric components undergoing heat sterilization, it is current practice to request that the extraction profile be obtained at 121°C/1 hour using an appropriate solvent. Compatibility: (for each component and/or the packaging system, as appropriate) • For coatings on metal tubes: Coating integrity testing • For elastomeric components: Evaluation of swelling effects • For plastic components (including tube coatings): USP Containers: Physicochemical Tests - Plastics testing • For ophthalmics: Particulate matter and eye irritants • Stability studies also support compatibility Performance: (For the assembled packaging system) • Functionality and/or drug delivery

Quality Control	<u>For Each Packaging System Received by the Applicant</u>: • Applicant's tests and acceptance criteria[c] • Dimensional (drawing) and performance criteria • Method to monitor consistency in composition of most plastic and elastomeric components (e.g., periodic comparison to the original extraction profile is recommended) <u>For Each Packaging Component Provided by the Supplier</u>: • Manufacturer's acceptance criteria for release, as appropriate • Description of the manufacturing process, as appropriate (e.g., procedure/validation for sterilization and depyrogenation)
Stability	• See section III.C.4

a. Including any additives used in the manufacture of a packaging component

b. Testing for plastics should be performed on the packaging component, not on the unformed resin.

c. Note that applicant's acceptance tests may include, among others, test parameters indicated under the description, suitability, and quality control sections of this table.

d Refer to the *Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug* (November 1994).

Table 5
AAO Recommended Color Coding of Caps and Labels for Topical Ophthalmic Medications

Class	Color	Pantone® Number
Anti-Infectives	Tan	467
Anti-Inflammatories/Steroids	Pink	197, 212
Mydriatics and Cycloplegics	Red	485C
Nonsteroidal Anti-Inflammatories	Gray	4C
Miotics	Green	374, 362, 348
Beta-Blockers	Yellow or Blue[a] Yellow C	290, 281
Adrenergic Agonists (e.g., Propine)	Purple	2583
Carbonic Anhydrase Inhibitors	Orange	1585
Prostaglandin Analogues	Turquoise	326C

a The AAO notes that as new classes of drugs are developed this coding system may be modified in the future by reassigning the blue color to a new class of drugs while keeping yellow for beta-blockers.

F. Liquid-Based Oral and Topical Drug Products and Topical Delivery Systems

A wide variety of drug products fall into this category. The presence of a liquid phase implies a significant potential for the transfer of materials from a packaging component into the dosage form. The higher viscosity of semisolid dosage forms and transdermal systems may cause the rate of migration of leachable substances into these dosage forms

to be slower than for aqueous solutions. Due to extended contact, the amount of leachables in these drug products may depend more on a leachable material's affinity for the liquid/semisolid phase than on the rate of migration.

1. Liquid-Based Oral Drug Products

Typical liquid-based oral dosage forms are elixirs, emulsions, extracts, fluid extracts, solutions, gels, syrups, spirits, tinctures, aromatic waters, and suspensions. These products are usually nonsterile but may be monitored for changes in bioburden or for the presence of specific microbes.

These dosage forms are generally marketed in multiple-unit bottles or in unit-dose or single-use pouches or cups. The dosage form may be used as is or admixed first with a compatible diluent or dispersant. A bottle is usually glass or plastic, often with a screw cap with a liner, and possibly with a tamper-resistant seal or an overcap that is welded to the bottle. The same cap liners and inner seals are sometimes used with solid oral dosage forms. A pouch may be a single-layer plastic or a laminated material. Both bottles and pouches may use an overwrap, which is usually a laminated material. A single-dose cup may be metal or plastic with a heat-sealed lid made of a laminated material.

A liquid-based oral drug product typically needs to be protected from solvent loss, microbial contamination, and sometimes from exposure to light or reactive gases (e.g., oxygen).

For glass components, data showing that a component meets the requirements of USP Containers: Glass Containers are accepted as sufficient evidence of safety and compatibility. For LDPE components, data from USP Containers tests are typically considered sufficient evidence of compatibility. The USP General Chapters do not specifically address safety for polyethylene (HDPE or LDPE), polypropylene (PP), or laminate components. A patient's exposure to substances extracted from a plastic packaging component (e.g., HDPE, LDPE, PP, laminated components) into a liquid-based oral dosage form is expected to be comparable to a patient's exposure to the same substances through the use of the same material when used to package food. Based on this assumption, an appropriate reference to the indirect food additive regulations (21 CFR 174-186)[20] is typically considered sufficient to establish safety of the material of construction, provided any limitations specified in the regulations are taken into consideration. This assumption is considered valid for liquid-based oral dosage forms which the patient will take only for a relatively short time (acute dosing regimen).

[20] See Attachment A for a listing of the FDA regulations for indirect food additives.

For liquid-based oral drug products which the patient will continue to take for an extended period (i.e., months or years (chronic drug regimen)), a material of construction that meets the requirements for indirect food additives will be considered safe — on that basis alone — only if the patient's exposure to extractables can be expected to be no greater than the exposure through foods, or the length of exposure is supported by toxicological information. For example, if the dosage form is aqueous-based and contains little or no cosolvent (or other substance, including the active drug substance, liable to cause greater extraction of substances from plastic packaging components than would be extracted by water), meeting the requirements of the indirect food additive regulations will usually satisfy the issue of safety.

If the dosage form contains cosolvents (or if, for any reason, it may be expected to extract greater amounts of substances from plastic packaging components than water), then additional extractable information[21] may be needed to address safety issues.

Performance is typically not a factor for liquid-based oral drug products.

See Table 6 for additional information.

2. Topical Drug Products

Topical dosage forms include aerosols, creams, emulsions, gels, lotions, ointments, pastes, powders, solutions, and suspensions. These dosage forms are generally intended for local (not systemic) effect and are generally applied to the skin or oral mucosal surfaces. Topical products also include some nasal and otic preparations as well as some ophthalmic drug products. Ophthalmic drug products are discussed in section III.E.2. Vaginal and rectal drug products may be considered to be topical if they are intended to have a local effect. Some topical drug products are sterile or may be subject to microbial limits. In these cases, additional evaluation may be necessary when determining the appropriate packaging.

A liquid-based topical product typically has a fluid or semi-solid consistency and is marketed in a single- or multiple-unit container (e.g., a rigid bottle or jar, a collapsible tube, or a flexible pouch). A powder product may be marketed in a sifter-top container. An antibacterial product may be marketed as part of a sterile dressing. There are also a number of products marketed as a pressurized aerosol or a hand-pumped spray.

A rigid bottle or jar is usually made of glass or polypropylene with a screw cap.

[21] See Attachment C for a discussion of extraction studies.

The same cap liners and inner seals are sometimes used as with solid oral dosage forms.

A collapsible tube is usually constructed from metal or is metal-lined, from LDPE or from a laminated material. Tubes are identified as either *blind-end* or *open-end.* In the former, there is no product contact with the cap on storage. Usually, the size of the tube is controlled by trimming it to an appropriate length for the target fill volume. Fill volume is commonly determined as an in-process measurement using bulk density. Usually there is no cap liner, although the tube may have a liner. Aluminum tubes usually include a liner. A tube liner is frequently a lacquer or shellac whose composition should be stated. A tube is closed by folding or crimping the open end. The type of fold (roll or saddle) should be described, as well as the type and composition of any sealant. If the tube material is self-sealing through the application of heat alone, this should be stated. If the market package includes a separate applicator device, this should be described. Product contact is possible if the applicator is part of the closure, and therefore an applicator's compatibility with the drug product should be established, as appropriate.

Dressings consist of dosage form on a bandage material (e.g., Absorbent Gauze USP or Gauze Bandage USP) within a flexible pouch. The pouch should maintain the sterility and physical stability of the dressing.

Unlike inhalation aerosols, topical aerosols are not intended to be inhaled. The droplet size of the spray does not need to be carefully controlled, nor is the dose usually metered. The spray may be used to apply dosage form to the skin (topical aerosol) or mouth (lingual aerosol) and functionality of the sprayer should be addressed. A topical aerosol may be sterile or may conform to acceptance criteria for microbial limits.

The packaging system for a liquid-based topical product should deter solvent loss and should provide protection from light when appropriate. Because these dosage forms may be placed in contact with mucosal membranes or with skin that has been broken or otherwise compromised, the safety of the materials of construction for the packaging components should be evaluated. For liquid and semisolid dosage forms, the same information as described in section III.F.1 is accepted for establishing safety and compatibility. For solid dosage forms, an appropriate reference to the indirect food additive regulations is typically considered sufficient to establish safety.

See Table 6 for additional information.

3. Topical Delivery Systems

Topical delivery systems are self-contained, discrete dosage forms that are

designed to deliver drug via intact skin or body surface. USP Pharmaceutical Dosage Forms defines three types of topical delivery systems: transdermal, ocular, and intrauterine.

Transdermal systems are usually applied to the skin with an adhesive and may be in place for an extended period. Ocular systems are inserted under the lower eyelid, typically for seven days. Intrauterine systems are held in place without adhesive and may stay in place for a year.

A transdermal system is usually comprised of an outer barrier, a drug reservoir (with or without a rate-controlling membrane), a contact adhesive, and a protective liner. An ocular system usually consists of the drug formulation contained in a rate-controlling membrane. An intrauterine system may be constructed of a plastic material impregnated with active ingredients or a coated metal. It is shaped to remain in place after being inserted in the uterus.

Each of these systems is generally marketed in a single-unit soft blister pack or a preformed tray with a preformed cover or overwrap.

Compatibility and safety for topical delivery systems are addressed in the same manner as for topical drug products. Performance and quality control should be addressed for the rate-controlling membrane. Appropriate microbial limits should be established and justified for each delivery system. Microbiological standards are under development; therefore the review division for a specific application should be consulted.

See Table 6 for additional information.

Table 6
Information That Typically Should Be Submitted for Liquid-Based Oral and Topical Drug Products and for Topical Drug Delivery Systems

Description	Overall general description of container closure system, plus: For Each Packaging Component: • Name, product code, manufacturer, physical description • Materials of construction (for each: name, manufacturer and product code) • Description of any additional treatments (e.g., procedure for washing components)
Suitability	Protection: (by each component and/or the container closure system, as appropriate) • Light exposure • Reactive gases (e.g., oxygen) • Solvent loss • Moisture permeation (liquid-based oral products would typically meet USP requirements for a tight or class A container) • Microbial contamination (container integrity, increased bioburden, microbial limits, as appropriate) • Seal integrity or leak testing of tubes (topical drug products) and unit dose containers (liquid-based oral drug products) Safety: (for each material of composition, as appropriate) • Chemical composition of all plastics, elastomers, adhesives, etc.[a] • For most liquid-based oral drug products: appropriate reference to the indirect food additive regulations • For liquid-based oral drug products with chronic dosing regimens that contain alcohol or a cosolvent: information to establish that exposure to extractables will be no greater than that expected to result from the use of similar packaging components when used with foods,[b] or that the exposure is acceptable based on toxicological data. • For topical drug products (plastic coatings for metal tubes), and plastic drug delivery system components: USP Containers testing • For topical delivery systems: appropriate reference to indirect food additive regulations Compatibility: (for each component of the packaging system, as appropriate) • For LDPE and glass components, USP Containers testing[c] • For coatings for metal tubes: coating integrity testing Performance: (for the assembled packaging system) • Functionality and/or drug delivery should be addressed, as appropriate.
Quality Control	For Each Packaging Component Received by the Applicant: • Applicant's tests and acceptance criteria[d] • Dimensional (drawing) and performance criteria • Method to monitor consistency in composition, as appropriate For Each Packaging Component Provided by the Supplier: • Manufacturer's acceptance criteria for release, as appropriate • Description of the manufacturing process, as appropriate

Stability	• See section III.C.4

[a] Including any additives used in the manufacture of a packaging component

[b] The materials of construction should be acceptable for contact with foods that have extraction characteristics similar to those of the drug product (e.g., aqueous, acidic, alcoholic, or fatty).

[c] Plastics testing should be performed on the packaging component, not on the unformed resin.

[d] Note that applicant's acceptance tests may include, among others, test parameters indicated under the description, suitability, and quality control sections of this table.

G. Solid Oral Dosage Forms and Powders for Reconstitution

The most common solid oral dosage forms are capsules and tablets. For the purpose of this guidance, oral powders and granules for reconstitution are also included in this group.

The risk of interaction between packaging components and a solid oral dosage form is generally recognized to be small. Powders that are reconstituted in their market container, however, have an additional possibility of an interaction between the packaging components and the reconstituting fluid. Although the contact time will be relatively short when compared to the component/dosage form contact time for liquid-based oral dosage forms, it should still be taken into consideration when the compatibility and safety of the container closure system is being evaluated.

A typical container closure system is a plastic (usually HDPE) bottle with a screw-on or snap-off closure and a flexible packaging system, such as a pouch or a blister package. A typical closure consists of a cap, often with a liner, and frequently with an inner seal. If used, fillers, desiccants, and other absorbent materials are considered primary packaging components.

The most common forms of flexible packaging are the blister package and the pouch. A blister package usually consists of a lidding material and a forming film. The lidding material is usually a laminate which includes a barrier layer (e.g., aluminum foil) with a print primer on one side and a sealing agent (e.g., a heat-sealing lacquer) on the other side. The sealing agent contacts the dosage form and the forming film. The forming film may be a single film, a coated film, or a laminate. A pouch typically consists of film or laminate which is sealed at the edges by heat or adhesive. Leak testing is usually performed on flexible packages as part of the in-process controls.

Solid oral dosage forms generally need to be protected from the potential adverse affects of water vapor. Protection from light and reactive gases may also be needed. For example the presence of moisture may affect the decomposition rate of the active drug substance or the dissolution rate of the dosage form. The container should have an intrinsically low rate of water vapor permeation, and the container closure system should establish a seal to protect the drug product. Three standard tests for water vapor permeation have been established by the USP for use with solid oral dosage forms.

1. Polyethylene Containers (USP <661>): This test is conducted on containers heat-sealed with foil laminate; therefore only the properties of the container are evaluated. The level of protection from water vapor permeation provided by a packaging system marketed with a heat-sealed foil laminate inner seal (up to the time the inner seal is removed) is expected to be approximately the same as that determined by this test. The acceptance criteria are those established in USP <671>.

2. Single-Unit Containers and Unit-Dose Containers for Capsules and Tablets (USP <671>): This test measures the water vapor permeation of a single-unit or unit-dose container closure system and establishes acceptance criteria for five standards (*Class A-E* containers).

3. Multiple-Unit Containers for Capsules and Tablets (USP <671>): This test is intended for drugs being dispensed on prescription, but has also been applied to the drug product manufacturer's container closure system. If the container closure system has an inner seal, it should be removed prior to testing. The results from this study reflect the contributions to water vapor permeation through the container, and through the seal between the container and the closure. Acceptance criteria have been established for two standards (*tight* and *well-closed* containers).

For solid oral dosage forms, a reference to the appropriate indirect food additive regulation for each material of construction is typically considered sufficient evidence of safety. However, for a powder for reconstitution dosage form, reference only to the indirect food additive regulations as evidence of safety for the materials of construction is not recommended. Compatibility for solid oral dosage forms and for powders for reconstitution is typically addressed for plastics and glass by meeting the requirements of the USP Containers test.

The USP monographs for Purified Cotton and Purified Rayon will typically be considered sufficient standards to establish the safety of these materials as fillers in the packaging of tablets or capsules, with the following caveats: cotton need not meet the monograph requirements for sterility, fiber length, or absorbency; and rayon need not meet the monograph requirements for fiber length or absorbency. Appropriate tests and acceptance criteria for identification and for moisture content should be provided for both cotton and rayon filler. Rayon has been found to be a potential source of dissolution problems for gelatin capsules and gelatin-coated tablets and this characteristic should be considered when choosing a filler.[22] The use of other fillers may be considered with appropriate tests and acceptance criteria.

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[22] Hartauer, K.J. et al., "The Effects of Rayon Coiler on the Dissolution Stability of Hard Shelled Gelatin Capsules," *Pharmaceutical Technology,* 17:76-83 (1993).

If a desiccant or other absorbent material is used, the composition should be provided (or an appropriate DMF referenced). The component should differ in shape and/or size from the tablets or capsules with which it is packaged. This will help distinguish between the component and the dosage form. Because these are considered primary packaging components, appropriate tests and acceptance criteria to establish suitability should be provided (see Table 7 for additional information).

Table 7
Information That Typically Should Be Submitted for Solid Oral Drug Products and Powders

Description	Overall general description of container closure system, plus: For Each Packaging Component: • Name, product code, manufacturer • Materials of construction • Description of any additional treatments
Suitability	Protection: (by each component and/or the container closure system, as appropriate) • Light exposure • Moisture permeation • Seal integrity or leak tests for unit-dose packaging Safety: (for each material of construction, as appropriate) • Chemical composition of all plastics, elastomers, adhesives, etc.[a] • For tablets, capsules, and powders, appropriate reference to the indirect food additive regulation may be submitted, but may not be appropriate for Powders for Reconstitution. • For rayon and cotton fillers, data from USP monographs. For non-USP materials, data and acceptance criteria should be provided. • For dessicants and other absorbent materials: the size and shape should differ from that of the dosage form. Compatibility: (on each component or the packaging system) • For glass and plastic containers, data from USP Containers[b] testing. Performance: (on each component or the packaging system, as appropriate) • Functionality and/or drug delivery, as appropriate
Quality Control	For Each Packaging Component Received by the Applicant: • Applicant's tests and acceptance criteria[c] • Dimensional (drawing) and performance criteria • Method to monitor consistency in composition, as appropriate For Each Packaging Component Provided by the Supplier: • Manufacturer's acceptance criteria for release, as appropriate • Description of manufacturing process, as appropriate
Stability	• See section III.C.4

[a] Including any additives used in the manufacture of a packaging component

[b] Testing of plastics should be performed on the packaging component, not on the unformed resin.

[c] Note that applicant's acceptance tests may include, among others, test parameters indicated under the description, suitability, and quality control sections of this table.

H. Other Dosage Forms

The CGMP requirements for container closure systems for compressed medical gases are described in 21 CFR 210 and 211. The containers are regulated by the U.S. Department of Transportation. For more detailed information refer to the CDER *Compressed Medical Gas Guideline* (February 1989).

When submitting information for a drug product or dosage form not specifically covered by the sections above, a firm should take into consideration: (1) the compatibility and safety concerns raised by the route of administration of the drug product and the nature of the dosage form (e.g., solid or liquid-based); (2) the kinds of protection the container closure system should provide to the dosage form; and (3) the potential effect of any treatment or handling that may be unique to the drug product in the packaging system. Quality control procedures for each packaging component should ensure the maintenance of the safety and quality of future production batches of the drug product.

IV. POSTAPPROVAL PACKAGING CHANGES

For an approved application (NDA, ANDA or BLA), a change to a container closure system, to a component of the container closure system, to a material of construction for a component, or to a process involving one of the above must be reported to the application. The filing requirements are specified under 21 CFR 314.70 (supplements and other changes to an approved application) for an NDA or ANDA, and under 21 CFR 601.12 (changes to an approved application) for a BLA. The submission should address the items described and discussed in sections III.B and III.C of this guidance. The Agency intends to provide additional guidance on postapproval changes in container closure systems in the future.

V. TYPE III DRUG MASTER FILES

A. General Comments

The responsibility for providing information about packaging components rests foremost with the applicant of an NDA, ANDA or BLA, or the sponsor of an IND. This information may be provided to the applicant by the manufacturer of a packaging component or material of construction and may be included directly in the application. Any information that a manufacturer does not wish to share with the applicant or sponsor (i.e., because it is considered proprietary) may be placed in a Type III DMF and incorporated into the application by a letter from the manufacturer to the applicant which authorizes reference to the DMF. The letter of authorization should specify the firm to whom authorization is granted, the component or material of construction being described, and where the information and/or data is located in the file by page number and/or date of submission. This last item is especially important for files that contain information on multiple components or have several volumes.

Information in a Type III DMF is not restricted to data of a proprietary nature. DMF holders may include in their files as much or as little information as they choose. In addition, a manufacturer of a packaging component is not required to maintain a Type III DMF. Without a DMF there is no procedure for the Agency to review proprietary information except by submission to the application.

The Agency ordinarily reviews a DMF only in connection with an application (IND, NDA, ANDA, or BLA). If the combined information from the application and the DMF is not adequate to support approval of the application or safety for the IND, then the Agency may request additional information from the applicant and/or the DMF holder, as appropriate.

In the event of a change in the DMF, the holder of a DMF must notify the holder of each application supported by the DMF (21 CFR 314.420(c)). Notice should be provided well before the change is implemented to allow the applicant or sponsor enough time to file a supplement or an amendment to the affected application.

General information on format and content of a DMF and a LOA may be found in the CDER *Guideline for Drug Master Files* (September 1989).

B. Information in a Type III DMF

Section III of this guidance describes the kind of descriptive, suitability, and quality control information which the Agency usually reviews concerning packaging components and materials of construction for drug products. The following are examples of the items that have been submitted via a Type III DMF.

1. Descriptive Information:

    a. General description of the component and the address of the manufacturing site

    b. Description of the manufacturing process for a packaging component and operations performed after manufacture, but prior to shipment (washing, coating, sterilization or depyrogenation)

    c. Description of the acceptance, in-process, and release controls for materials of construction, the manufacturing process, and the finished product (component part or assembled component)

    d. Characterization of the key properties

2. Information About Suitability

a. Protection provided by the component

b. Safety information on the materials of construction or the finished component

c. Compatibility of the materials of construction or the finished component with the specific dosage form, the specific drug product, or equivalent materials

3. Information About Quality Control:

a. Dimensional (an engineering drawing) and performance criteria for the component

b. A description of the quality control measures used to maintain consistency in the physical and chemical characteristics of packaging components

c. A summary of the quality assurance/quality control criteria when release of the component is based on statistical process control

VI. BULK CONTAINERS

A. Containers for Bulk Drug Substances

Drug substances are generally solids, but some are liquids or gases.

The container closure system for storage or shipment of a bulk solid drug substance is typically a drum with double LDPE liners that are usually heat sealed or closed with a twist tie. A desiccant may be placed between the bags.

The drum provides protection from light and mechanical strength to protect the liner during shipment and handling. The majority of the protection from air and moisture is provided by the liner. Because LDPE is not a particularly good moisture barrier, a drug substance that is moisture sensitive may need additional protection. An alternative to a LDPE bag is a heat-sealable laminate bag with a comparatively low rate of water vapor transmission.

Qualification of the packaging system is usually based on establishing compatibility and safety of the liner but may also include characterization for solvent or gas transmission (see section III.B).

The container closure system for the storage or shipment of a bulk liquid drug substance is typically plastic, stainless steel, a glass-lined metal container, or an epoxy-lined metal

container with a rugged, tamper-resistant closure. Qualification of the container closure system may include characterization for solvent and gas permeation, light transmittance, closure integrity, ruggedness in shipment, protection against microbial contamination through the closure, and compatibility and safety of the packaging components as appropriate (see section III.B).

The application (or Type II DMF) should include a detailed description of the complete container closure system for the bulk drug substance as well as a description of the specific container, closure, all liners, inner seal, and desiccant (if any), and the composition of each component. A reference to the appropriate indirect food additive regulation is typically considered sufficient to establish the safety of the materials of construction (also note the discussion on this subject in section III). The tests, methods, and criteria for the acceptance and release of each packaging component should be provided.

Stability studies to establish a retest period for bulk drug substance in the proposed container closure system should be conducted with fillers or desiccant packs in place (if used). Smaller versions which simulate the actual container closure system may be used. Stability recommendations for container closure systems of different types are described in the *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987).[23]

Container closure systems for compressed medical gases are discussed in section III.H.

B. Containers for Bulk Drug Products

A container closure system for bulk drug products may be used for storage prior to packaging or for shipment to repackagers or contract packagers. In all cases, the container closure system should adequately protect the dosage form and should be constructed of materials that are compatible and safe.

Container closure systems for on-site storage have generally been considered a CGMP issue under 21 CFR 211.65. However, if a firm plans to hold bulk drug products in storage, then the container closure system and the maximum storage time should be described and justified in the application. In addition, stability data should be provided to demonstrate that extended storage in the described containers does not adversely affect the dosage form. Even when the storage time before packaging will be short, a firm should use a container closure system that provides adequate protection and that is manufactured from materials that are compatible and safe for the intended use (see section III.B).

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[23] The 1987 stability guidance will be superseded by the FDA guidance for industry *Stability Testing of Drug Substances and Drug Products,* issued in draft for comment in June 1998, once it is issued in final form.

A container closure system for the transportation of bulk drug products to contract packagers (section II.C.3) should be described in the application. The container closure system should be adequate to protect the dosage form, be constructed with materials that are compatible with product being stored, and be safe for the intended use. The protective properties of the shipping container are verified by the practice of including annual batches of the packaged product in postapproval stability studies.

A container closure system specifically intended for the transportation of a large volume of drug product to a repackager (section II.C.3), whether for a solid or liquid dosage form, is considered a market package. The package should meet the same requirements for protection, compatibility, and safety as a smaller market package;[24] should be included in the stability studies for application approval and in the long term stability protocol; and should be fully described in the application. The length of time that the dosage form will spend in the bulk container may be a factor in determining the level of detail of the supporting information. Two examples of a large-volume shipping package are a 10,000-tablet HDPE pail with tamper-evident closure, and a 10-liter polyethylene terephthalate (PET) container with a screw cap closure with dispenser attachment for a liquid drug product. Both are intended for sale to a mass distribution pharmacy. A special case is the pharmacy bulk package which is described in USP <1>.

[24] FDA *Compliance Policy Guides*, "Regulatory Action Regarding Approved New Drugs and Antibiotic Drug Products Subjected to Additional Processing or other Manipulation," Section 446.100, January 18, 1991 (CPG 7132c.06).

ATTACHMENT A[25]

REGULATORY REQUIREMENTS

1. The Federal Food, Drug, and Cosmetic Act

a. Section 501

A drug or device shall be deemed to be adulterated "if its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health" (section 501(a)(3)); or "if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess (section 501(a)(2)(B)).

b. Section 502

A drug or device shall be deemed to be misbranded:

- "[i]f it purports to be a drug the name of which is recognized in an official compendium, unless it is packaged and labeled as prescribed therein" (section 502(g))

- "[i]f it is a drug and its container is so made, formed, or filled as to be misleading" (section 502(i)(1))

- "[i]f it is a drug and its packaging or labeling is in violation of an applicable regulation issued pursuant to section 3 or 4 of the Poison Prevention Packaging Act of 1970" (section 502(p))

c. Section 505

"No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug" (section 505(a)).

Section 505(b)(1)(D) requires "a full description of the methods used in, and the

[25] Applicants should check the appropriate sources directly for the most up-to-date information.

facilities and controls used for, the manufacture, processing, and packing of such drug."

2. The Code of Federal Regulations

a. 21 CFR 211 - Current Good Manufacturing Practice for Finished Pharmaceuticals

i. Subpart E, Control of Components and Drug Product Containers and Closures (21 CFR 211.80 - 211.94)

In particular, 21 CFR 211.94 outlines the requirements for drug product containers and closures:

(a) Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.

(b) Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.

(c) Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to ensure that they are suitable for their intended use.

(d) Standards or acceptance criteria, test methods, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures.

ii. Subpart F, Production and Process Controls (21 CFR 211.100 - 211.115)

iii. Subpart G, Packaging and Labeling Control (21 CFR 211.122 - 211.137)

In particular, 21 CFR 211.132 describes the tamper-resistant packaging requirements for over-the-counter (OTC) human drug products. Most OTC drug products must be packaged in tamper-resistant containers.

b. 16 CFR 1700-1702 - Special Packaging

The U.S. Consumer Product Safety Commission (CPSC) is responsible for enforcing the Poison Prevention Packaging Act of 1970 (PPPA). The PPPA requires special packaging of hazardous household substances to protect children

from serious personal injury or serious illness from handling, using, or ingesting the substances. Drug products containing controlled substances, most human oral prescription drug products (including oral investigational drugs used in outpatient trials), and OTC drug preparations containing aspirin, acetaminophen, diphenhydramine, liquid methyl salicylate, ibuprofen, loperamide, lidocaine, dibucaine, naproxen, iron, or ketoprofen, require special packaging (16 CFR 1700.14).

Special packaging is defined under 15 U.S.C. 1471(2)(4), 16 CFR 1700.1(b)(4), and 21 CFR 310.3(l). Regulations issued under the PPPA establish performance standards and test methods that determine if a packaging system is child-resistant and adult-use-effective (16 CFR 1700.15 and 16 CFR 1700.20, respectively). Except as noted below, all PPPA-regulated substances must be in packaging systems that comply with these special packaging standards. The standards apply to both reclosable and nonreclosable packaging systems (unit-dose packaging).

There are several situations where child-resistant packaging for drug products is not required. Manufacturers and packagers of bulk-packaged prescription drug products do not have to use special packaging if the drug is intended to be repackaged by the pharmacist. However, the manufacturer or packager is responsible for child-resistant packaging if the drug product is intended to be dispensed to the consumer as packaged without repackaging by the pharmacist (16 CFR 1701.1). Prescribed drugs that are dispensed for use within institutions such as hospitals and nursing homes do not require child-resistant packaging. However, any prescriptions dispensed to patients upon their release for their use at home would be subject to the PPPA packaging requirements. In addition, drug product manufacturers are not required to provide child-resistant packaging for prescription drug samples that are distributed to physicians and other prescribing practitioners (i.e., physician samples).[26]

For OTC preparations, manufacturers or packagers are allowed to market one size in non-child-resistant packaging as long as child-resistant packages are also supplied. The non-child-resistant package requires special labeling (16 CFR 1700.5).

16 CFR 1702 establishes the procedures for petitioning the CPSC for an exemption from the PPPA requirements. Several prescription drugs (e.g., oral contraceptives in mnemonic packages, powdered colestipol, and medroxyprogesterone acetate) have been exempted from the special packaging requirements (16 CFR 1700.14(10)(I)-(xix)). The CPSC is permitted to grant an

[26] *Federal Register*, Volume 49, March 5, 1984, page 8008 (49 FR 8008), "Prescribed Drugs Distributed to Prescribing Practitioners; Withdrawal of Proposed Statement of Policy and Interpretation."

exemption if it finds that packaging is not required to protect children from serious injury, or that special packaging is not technically feasible, practicable, or appropriate for that product.

For additional information regarding these packaging requirements and the protocol test methods, please contact the CPSC. Their website is located at www.cpsc.gov and their hotline is 1-800-638-2772.

c. 21 CFR 174-186 - Indirect Food Additive Regulations

Regulations that are applicable to packaging components are:

i. Part 174 - Indirect Food Additives: General

ii. Part 175 - Indirect Food Additives: Adhesives and Components of Coatings

e.g.,	175.105	Adhesives
	175.300	Resinous and polymeric coatings

iii. Part 176 - Indirect Food Additives: Paper and Paperboard Components

e.g.,	176.170	Components of paper and paperboard in contact with aqueous and fatty foods
	176.180	Components of paper and paperboard in contact with dry food

iv. Part 177 - Indirect Food Additives: Polymers

e.g.,	177.1380	Fluorocarbon resins
	177.1520	Olefin polymers
	177.1630	Polyethylene phthalate polymers

v. Part 178 - Indirect Food Additives: Adjuvants, Production Aids, and Sanitizers

vi. Part 180 - Food Additives Permitted in Food or in Contact with Food on an Interim Basis Pending Additional Studies

e.g.,	180.22	Acrylonitrile copolymers

vii. Part 182 - Substances Generally Recognized as Safe

e.g.,	182.70	Substances migrating from cotton and cotton fabrics

		used in dry food packaging
	182.90	Substances migrating to food from paper and paperboard products

viii. Part 186 - Indirect Food Substances Affirmed as Generally Recognized as Safe (GRAS)

e.g., 186.1673 Pulp

d. Biologics Provisions, 21 CFR 600, Subpart B, Establishment Standards

i. 21 CFR 600.11(h) - Containers and Closures

ii. 21 CFR 601.2 - Applications for Licenses; Procedures for Filing

e. Other Sections

i. 21 CFR 201 - Labeling

ii. 21 CFR 310.509 - Parenteral drug products in plastic containers

iii. 21 CFR 200.50(a)(3) - Containers of ophthalmic preparations

3. U.S. Pharmacopeia/National Formulary

The following sections are applicable to packaging components:

a. General Notices - PRESERVATION, PACKAGING, STORAGE, AND LABELING

b. General Tests and Assays

<1>	Injections
<51>	Antimicrobial Preservatives - Effectiveness
<61>	Microbial Limit Tests
<71>	Sterility Tests
<87>	Biological Reactivity Tests, in vitro
<88>	Biological Reactivity Tests, in vivo
<161>	Transfusion and Infusion Assemblies
<381>	Elastomeric Closures for Injections • Biological Test Procedures • Physicochemical Test Procedures
<601>	Aerosols
<661>	Containers

- Light Transmission
- Chemical Resistance - Glass Containers
- Biological Tests - Plastics and Other Polymers
- Physicochemical Tests - Plastics
- Containers for Ophthalmics - Plastics
- Polyethylene Containers
- Polyethylene Terephthalate Bottles and Polyethylene Terephthalate G Bottles
- Single-Unit Containers and Unit-Dose Containers for Nonsterile Solid and Liquid Dosage Forms
- Customized Patient Medication Packages

<671> Containers - Permeation
- Multiple-Unit Containers for Capsules and Tablets
- Single-Unit Containers and Unit-Dose Containers for Capsules and Tablets

<691> Cotton (or the monograph for Purified Rayon USP)

<771> Ophthalmic Ointments

<1041> Biologics

<1151> Pharmaceutical Dosage Forms

ATTACHMENT B

COMPLIANCE POLICY GUIDES THAT CONCERN PACKAGING
(August 1996)

Compliance Policy Guides are issued by the Division of Compliance Policy (in the Office of Enforcement/Office of Regulatory Affairs). The following is a list of Compliance Policy Guides that concern packaging. Any questions or concerns about the content of any Compliance Policy Guide should be addressed to the Office of Enforcement/Office of Regulatory Affairs/Division of Compliance Policy at 301-827-0420 (telephone), 301-827-0482 (FAX) or www.fda.gov/ora/compliance_ref/cpg/default.html (Internet).

Sub Chapter 410	BULK DRUGS
Sec. 410.100	Finished Dosage Form Drug Products in Bulk Containers - Applications of Current Good Manufacturing Practice Regulations (CPG 7132a.06)
Sub Chapter 430	LABELING and REPACKAGING
Sec. 430.100	Unit Dose Labeling for Solid and Liquid Oral Dosage Forms (CPG 7132b.10)
Sec. 430.200	Repacking of Drug Products - Testing/Examination Under CGMPs (CPG 7132.13)
Sub Chapter 440-448	NEW DRUGS
Sec. 446.100	Regulatory Action Regarding Approved New Drugs and Antibiotic Drug Products Subjected to Additional Processing or Other Manipulations (CPG 7132c.06)
Sub Chapter 450-457	OTC
Sec. 450.500	Tamper-Resistant Packaging Requirements for Certain Over-the-Counter (OTC) Human Drug Products (CPG 7132a.17)
Sec. 450.550	Control and Accountability of Labeling Associated with Tamper-Resistant Packaging of Over-the-Counter Drug Products (CPG 7132.14)
Sub Chapter 480	STABILITY/EXPIRATION

Sec. 480.100	Requirements for Expiration Dating and Stability Testing (CPG 7132a.04)
Sec. 480.200	Expiration Dating of Unit Dose Repackaged Drugs (CPG 7132b.11)
Sec. 480.300	Lack of Expiration Date of Stability Data (CPG 7132a.10)

ATTACHMENT C

EXTRACTION STUDIES

An extraction study of a packaging component typically involves exposing a sample of the component, often subdivided into small pieces to increase surface area, to an appropriate solvent system at elevated temperatures, followed by chemical analysis. The purpose of elevated temperature is to increase the rate of extraction, so that a short experimental time may simulate a longer exposure time at room temperature, or to maximize the amount of extractables obtained from a sample.

The methods employed to analyze the resulting extracts vary, depending on the purpose of the extraction study and the nature of the packaging component. The extraction solvent may be evaporated to concentrate the extracts or to determine the total weight of nonvolatile extractables. Appropriate methods, such as HPLC or gas chromatography, may be used to obtain qualitative or quantitative extraction profiles of volatile or nonvolatile extractables.

Extraction studies may be conducted during the qualification of packaging components for any of the following purposes:

- To perform USP characterization tests on plastics (USP <661>) or elastomers (USP <381>)
- To perform USP Biological Reactivity Tests (USP <87> and <88>) on plastics or elastomers
- To obtain qualitative extraction profiles of plastics or elastomers
- To obtain quantitative extraction profiles of plastics or elastomers
- To evaluate whether the FDA indirect food additive regulations provide an adequate indicator of safety

Extraction studies may also be conducted on a routine basis as a quality control measure to monitor the chemical compositions of elastomeric or other packaging components.

The solvent that should be used in an extraction study depends on the purpose of the study. The ideal situation is for the extracting solvent to have the same propensity to extract substances as the dosage form, thus obtaining the same quantitative extraction profile. For this study, the preferred solvent would be the drug product or placebo vehicle. When feasible, the dosage form itself would be used. A stronger extracting solvent than the drug product would be used to obtain a qualitative extraction profile that would be used to establish quality control criteria.

ATTACHMENT D

ABBREVIATIONS

AAO	American Academy of Ophthalmology
ANDA	Abbreviated New Drug Application
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CFSAN	Center for Food Safety and Applied Nutrition
CGMP	Current Good Manufacturing Practice
CMC	Chemistry, Manufacturing, and Control
COA	Certificate of Analysis
CPSC	Consumer Product Safety Commission
DMF	Drug Master File
DPI	Dry Powder Inhaler
FDA	U.S. Food and Drug Administration (the Agency)
HDPE	High Density Polyethylene
IND	Investigational New Drug Application
LDPE	Low Density Polyethylene
LOA	Letter of Authorization
LVP	Large-Volume Parenteral
MDI	Metered Dose Inhaler
NDA	New Drug Application
PET	Polyethylene Terephthalate
PETG	Polyethylene Terephthalate G
PP	Polypropylene
PVC	Polyvinyl Chloride
QA	Quality Assurance
QC	Quality Control
SVP	Small-Volume Parenteral
USP/NF	U.S. Pharmacopeia/National Formulary

ATTACHMENT E

REFERENCES[27]

Center for Drug Evaluation and Research (CDER) Compressed Medical Gases Guideline (February 1989)

FDA *Guideline for Drug Master Files* (September 1989)

FDA *Guidance for Industry on the Submission of Documentation for the Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (November 1994)

FDA *Guidance for Industry on the Content and Format on Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well Characterized, Therapeutic, Biotechnology-Derived Products* (November 1995)

FDA *Guidance for Industry on the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use* (August 1996)

FDA *Guidance for Industry on the Submission of Chemistry, Manufacturing, and Controls Information and Establishment Description for Autologous Somatic Cell Therapy Products* (January 1997)

FDA *Guidance for the Photostability Testing of New Drug Substance and Products* (May 1997)

FDA *Guidance for Industry on the Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances* (January 1998)

FDA *Guidance for Industry on the Content and Format of Chemistry, Manufacturing, and Controls and Establishment Description Information for a Vaccine or Related Product* (January 1999)

FDA *Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls and Establishment Description Information for Human Plasma-Derived Biological Product or Animal Plasma or Serum-Derived Products* (February 1999)

FDA *Guidance for Industry on the Content and Format of Chemistry, Manufacturing, and*

[27] A list of CDER and CBER guidances and guidelines is provided on the Internet at www.fda.gov/cder/guidances.index.htm and www.fda.gov/cber/guidelines.htm, respectively.

Controls and Establishment Description Information for a Biological In Vitro Diagnostic Product (March 1999)

FDA *Guidance for Industry on the Content and Format of Chemistry, Manufacturing, and Controls and Establishment Description Information for Allergenic Extract or Allergen Patch Test* (April 1999)

FDA *Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and for the Completion of the FDA Form 356h, Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use* (May 1999)